In the Specification

On page 1, after the title and before line 5, please insert the following new paragraph:

This application is a continuation of U.S. Serial No. 09/671,100, filed September 27, 2000, which is a continuation of PCT International Application PCT/US99/07175 filed April 1, 1999, which is a continuation-in-part of U.S. Serial No. 09/053,871, filed April 1, 1998, now U.S. Patent No. 6,315,995 B1, issued November 13, 2001 which is a continuation-in-part of PCT International Application No. PCT/US97/17229, filed September 25, 1997, and a continuation-in-part of U.S. Serial No. 08/721,447, filed September 27, 1996, all of which applications are hereby incorporated by reference in their entireties into this application.

Please delete the paragraph on page 110, beginning at line 7 and insert the following paragraph:

Carbon monoxide gas, a toxic byproduct of heme catabolism, is involved in long-term potentiation and memory in the central nervous system. However, other physiologic roles for CO production in the brain are unknown. Because heme oxygenase is induced during inflammatory conditions, it was investigated whether endogenous CO production may confer a cerebral protective role in stroke. In a murine model of focal cerebral ischemia, heme oxygenase type I was induced at the mRNA (by Northern blot) and protein levels (by Western blot), localized to the cerebral vascular endothelium in the ischemic hemisphere by in situ

hybridization and immunohistochemistry (Figures 26 and 27). Local production of CO by direct measurement was observed in the ischemic zone. In parallel experiments, murine brain endothelial cells exposed to a hypoxic environment demonstrated similar induction of heme oxygenase mRNA, protein and CO generation (Figure 28). To determine whether CO production was incidental to the pathophysiology of stroke, CO production was blocked by tin protoporphyrin administration (confirmed by direct measurement of reduced local CO levels). These animals demonstrated significantly larger infarct volumes, worse neurological outcomes, and increased mortality compared with untreated controls (Figure 24). Furthermore, administration of CO prior to stroke conferred significant cerebral protection (Figure 23). As this protection was not observed in animals treated with biliverdin, the coincident byproduct of heme catabolism, these data suggest that endogenous CO production per se has a protective role in evolving stroke.

Please delete the paragraph on page 111, beginning at line 17 and insert the following paragraph:

The current study reports for the first time that the postischemic brain generates enormous quantities of CO. Using a murine model of focal cerebral ischemia in which the middle cerebral artery is occluded by an intraluminal suture, HOI production in the ischemic hemisphere was increased significantly in comparison to the nonischemic hemisphere (Figure 26). Because immunohistochemistry and in situ hybridization localized the source of HOI to endothelial cells within the ischemic hemisphere, an in vitro model of cellular hypoxia was used to confirm the

induction of HOI message, protein and activity in murine cerebral microvascular endothelial cells (Figures 29 and 30). Blockade of CO production using tin or zinc protoporphyrin IX was associated with an increase in cerebral infarct volume and mortality, whereas exposing animals to CO immediately prior to ischemia conferred significant dose-dependent cerebral protection within a narrow therapeutic window (Figure 24). Biliverdin administration was without effect in this model. Taken together, these data indicate that ischemic brain tissue produces large amounts of CO, the production of which confers cerebral protection that limits the amount of tissue destroyed during stroke.